



Application of kinetic modeling to predict the fate of two indoxacarb metabolites and their bound residues in soil



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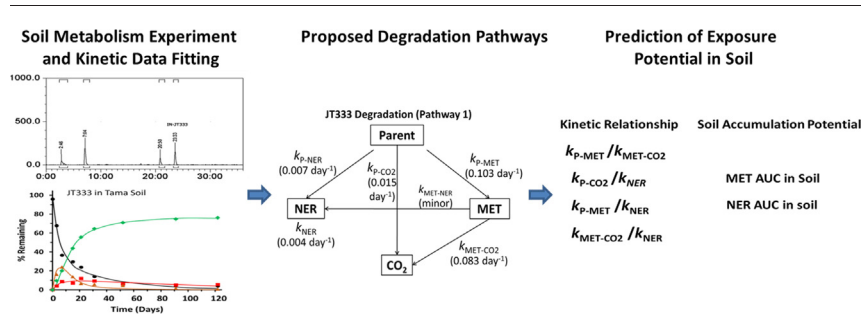
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HIGHLIGHTS

- Adsorption and metabolism of two of the indoxacarb metabolites determined in soils
- Inverse kinetic models were fit to the rate of degradation data.
- Application of kinetic modeling to elucidate metabolic pathway in soil
- Application of kinetic model for NER degradation analysis
- Discussion on the potential of NER kinetic modeling in environmental risk assessment

GRAPHICAL ABSTRACT



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ABSTRACT

Insecticide indoxacarb metabolites JT333 and MP819 were used as model compounds to assess the utilization of kinetic modeling to elucidate metabolic pathways, determine degradation kinetics of non-extractable residues (NER) and predict the accumulation potential of the released NER in soil. Soil adsorption coefficients and degradation product formation were determined in different soils in laboratory. Inverse kinetic modeling was applied to explore the dynamics of dissipation of parent (P), formation of extractable metabolites (MET), NER and CO₂, and to identify their routes of degradation in soil. These two compounds share similar structural characteristics, have high affinity to soil ($K_{oc} > 5000$ L/kg), short half-life (DT_{50} of 4–9 days), and significant CO₂ formation in soil. However, kinetic modeling showed that they degraded via different pathways. The P-MET-CO₂ conversion route was the major degradation pathway for JT333 in aerobic soil. Multiple pathways were involved in MP819 degradation, while the formation of NER was predominant. The time-exposure area under the curves (AUC) for the MET or NER in soils were derived from the time-%concentration plots for the evaluation of rate limiting steps in their degradation pathways. In P-MET-CO₂ pathway the MET-CO₂ conversion is the rate limiting step for both compounds. Higher P-MET conversion/MET-CO₂ conversion rate constant ratio resulted in larger MET AUC. The rate of NER degradation appeared much slower compared to the rates of P-MET and MET-CO₂ conversions, likely due to the rate-limiting step of NER release from the bound-state, indicating that in this situation the free-state NER would be unlikely to accumulate in soil. The study reported here demonstrates the utility of kinetic modeling to quantify the dynamics of NER formation/dissipation vs. P-MET-CO₂ conversion, and the application of kinetic modeling to predict the possibility of free-state NER accumulation in soil, therefore, reveals the potential for the quantitative NER environmental risk assessment.

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Abbreviations: AUC, area under the curve; % AR, percentage of applied radioactivity; DT_{50} , time for a concentration to decrease 50%; OC, organic carbon; K_d , soil adsorption coefficient; K_{oc} , soil adsorption coefficient normalized for percent organic carbon; LSC, liquid scintillation counting; P, parent compound; MET, extractable metabolites; NER, non-extractable residue.

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1. Introduction

For decades, pesticide metabolic fate, especially the fate of bound residue in soil, has been the special interest of pesticide environmental risk assessments because of unsettling debates on the potential long term impact of the bound residue to the environment. Upon application to the soil, pesticides can be metabolized and eventually mineralized to CO₂ by soil microorganisms, while part of the parent or metabolites can be bound to the soil and not extractable by organic solvents. This part of bound residue, also referred to as non-extractable residues (NER), is classified into types I, II, and III NER (Kästner et al., 2014). NER can be the parent compound and/or its degradation products (Mordault et al., 2005; Dec et al., 1997; Senesi, 1992). Depending on the degradation pathway, NER can also be separated into xenobiotic or biogenic (Nowak et al., 2013). Xenobiotic NERs are associated with type I and II NERs that are entrapped in the clay minerals in cavities between organic macromolecules (type I), or chemically bound to macromolecules (type II). Biogenic NERs are related to type III NERs as a result of soil microorganisms metabolizing and incorporating the parent or its metabolites into microbial biomass which are eventually mineralized to CO₂ (Poßberg et al., 2016; Kästner et al., 2014; Nowak et al., 2013). It is still arguable whether the formation of NER minimizes or potentiates long term environmental risks (Umeh et al., 2017; Barriuso et al., 2008; Jones et al., 2000). One opinion considers NER as 'hidden' parent or its metabolites capable of subsequent release and exertion of long-term biological and ecological effects (Kästner et al., 2014; Gevao et al., 2000; Scheunert and Schröder, 1998). The other argues that NER possesses no risk to the environment because it either becomes biogenic or as the xenobiotics that allows the slow-degrading compound in the bound state and becomes unavailable resulting in no short- or long term problems (Kearney, 1976; Alexander, 2000; Gevao et al., 2000; Reid et al., 2000).

While ¹⁴C-label tracers are widely used to trace the degradation products and monitor the formation of NERs, the nature of residues in the bound state and their degradation pathways remain to be fully identified. Furthermore, it is difficult to quantify the risk of NER by simply considering categorically the 'bound' and 'unbound' since the bound and free forms of NER are in dynamic equilibrium. An alternative approach was reported to use kinetic modeling to illustrate the dynamic relationship between parent and metabolites and their ultimate fate as NER and CO₂ (Boesten et al., 2006). Instead of identifying individual metabolite formation and degradation pathway, the initial kinetics model treats the system as three component pools: parent, extractable metabolites, and a combination of NER/CO₂ as the terminal product. The modeling of the experimental data enables the kinetic fitting to support the metabolic pathway elucidation. Because NER and CO₂ are grouped in the same component-pool, this model is unable to perform the kinetic analyses of NER formation and degradation. This inverse modeling approach was later refined by separating the system into four-component pools, parent, metabolite, NER, and CO₂ (Loos et al., 2012; Matthies et al., 2008). This four-pool compartment model was also used in elucidating Pyrethrin Sodium and its degradation pathway in soil (Sharma et al., 2016). It remains to be explored the potential of kinetic modeling in assessing the dynamics of NER exposure and in quantifying its risk to the environment.

Indoxacarb is a reduced risk broad spectrum insecticide (Galvan et al., 2005; Wing et al., 2000). Its metabolism and environmental fate have been extensively investigated (FAO and WHO, 2005). The insecticidal effect of indoxacarb is activated by the conversion to its active metabolite JT333 (Fig. 1) once inside the insect (Wing et al., 2000). JT333 can also be generated in soil (FAO and WHO, 2005). In this investigation using JT333 as the test compound, an inverse modeling approach was adapted to fit the JT333 soil degradation data to determine if a prediction model could be developed to elucidate its degradation and mineralization pathways, including the degradation pathway of NER in soil. Another indoxacarb metabolite, MP819 which shares similar structural

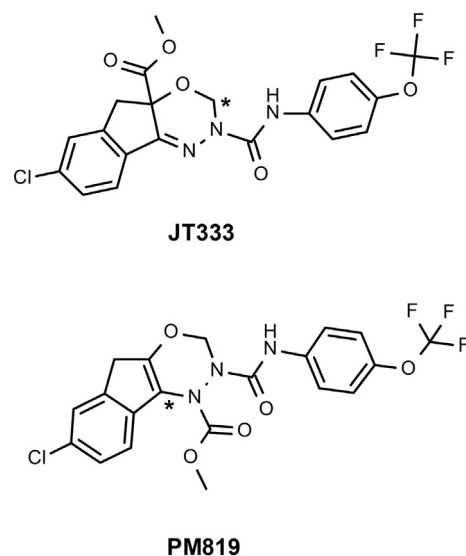


Fig. 1. Chemical structure of JT333 and MP819. *Denotes the site of ¹⁴C label.

characteristics with JT333 (Fig. 1) was also used in the study for comparison. The study reported in this manuscript explored the application of inverse kinetic modeling to elucidate the metabolic pathways, especially to quantify the rate limiting step of mineralization and NER dissipation. The application potential of inverse kinetic modeling for the NER environmental risk assessment is also discussed.

2. Material and methods

2.1. Target compounds and materials

Test materials JT333, methyl 7-chloro-2-[[4-(trifluoromethoxy)phenyl]amino]carbonyl]indeno[1,2-e][1,3,4]oxadiazine-4a(3H)-carboxylate, and MP819, methyl 7-chloro-2-[[4-(trifluoromethoxy)phenyl]carbamoyl]-3,5-dihydroindeno[1,2-e][1,3,4]oxadiazine-1-carboxylate, were synthesized at DuPont Company (Wilmington, DE). ¹⁴C-labeled JT333 (33.57 µCi/mg) and MP819 (57.5 µCi/mg) were synthesized by PerkinElmer (Boston, MA). Soils were freshly collected from multiple locations. Prior to use, each test soil was sieved through a 2 mm mesh sieve. The soils were stored at approximately 4 °C in the dark in closed bags when not in use. The full soil characterization is provided in supplementary materials.

All chemicals were reagent grade or purer and were purchased from Fisher Scientific (Waltham, MA) or Sigma-Aldrich (St. Louis, MO). Ultima Gold™ scintillation cocktail for Liquid scintillation counting (LSC) was from Perkin Elmer (Waltham, MA). Harvey™ Carbon 14 Cocktail used for samples combustion analysis was from (R.J. Harvey, Tappan, NY). LabLogic FlowLogic U Cocktail used for radioactive HPLC samples was from LabLogic (Brandon, FL).

2.2. Adsorption of test compounds to soils

An adsorption/desorption study was conducted with JT333 and MP819 to determine the soil adsorption coefficient (K_d) values. Four soils were used for the JT333 study and three soils were used for MP819. The JT333 and MP819 concentration in the CaCl₂ solution was 12 ppb and 20 ppb, respectively. The soil to solution ratio was 1:24, w/v for JT333 and 1:40, w/v for MP819.

2.2.1. JT333

The ¹⁴C-JT333 treatment solution was prepared by transferring 200-µL aliquot of 10 ppm ¹⁴C-JT333 acetonitrile stock solution into to a glass container. After the solvent was evaporated, 175-mL of 0.01 M CaCl₂

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